Pre-stroke CHA_2DS_2-VASc score and severity of acute stroke in patients with atrial fibrillation: findings from RAF study

Monica Acciarresi MD[1], Maurizio Paciaroni MD[1], Giancarlo Agnelli MD[1], Nicola Falocci, PhD[1], Valeria Caso MD, PhD[1], Cecilia Becattini MD[1], Simona Marcheselli MD[2], Christina Rueckert MD[3], Alessandro Pezzini MD[4], Andrea Morotti MD[4], Paolo Costa MD[4], Alessandro Padovani MD, PhD[4], Laszló Csiba MD[5], Lilla Szabó MD[5], Sung-Il Sohn MD, PhD[6], Tiziana Tassinari MD[7], Azmil H Abdul-Rahim MD[8], Patrik Michel, PD-MER[9], Maria Cordier MD[9], Peter Vanacker MD[10], Suzette Remillard MD[9], Andrea Alberti MD[1], Michele Venti MD, PhD[1], Cataldo D'Amore MD[1], Umberto Scoditti MD[11], Licia Denti MD[12], Giovanni Orlandi MD[13], Alberto Chiti MD[13], Gino Gialdini MD[13], Paolo Bovi MD[14], Monica Carletti MD[14], Alberto Rigatelli MD[14], Jukka Putaala MD[15], Turgut Tatlisumak MD[15,16], Luca Masotti MD[17], Gianni Lorenzini MD[17], Rossana Tassi MD[18], Francesca Guideri MD[18], Giuseppe Martini MD[18], Georgios Tsivgoulis MD[19,20,21], Kostantinos Vadikolias MD[19], Chrissoula Liantinioti MD[21], Francesco Corea MD, PhD[22], Massimo Del Sette MD[23], Walter Ageno MD[24], Maria Luisa De Lodovici MD[25], Giorgio Bono MD[25], Antonio Baldi MD[26] , Sebastiano D'Anna MD[26], Simona Sacco MD[27], Antonio Carolei[27], Cindy Tiseo MD[27], Davide Imberti MD[28], Dorjan Zabzuni MD[28], Boris Doronin MD[29], Vera Volodina MD[29], Domenico Consoli MD[30], Franco Galati MD[30], Alessio Pieroni MD[31], Danilo Toni MD, PhD[31], Serena Monaco MD[32], Mario Maimone Baronello MD[32], Kristian Barlinn MD[33], Lars-Peder Pallesen MD[33], Jessica Kepplinger MD[33], Ulf Bodechtel MD[33], Johannes Gerber MD[33], Dirk Deleu, MD[34], Gayane Melikyan MD[34], Faisal Ibrahim MD[34], Naveed Akhtar MD[34], Maria Giulia Mosconi MD[1], Kennedy R Lees MD[8]

[1]Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Italy
[2]Neurologia d'urgenza e Stroke Unit, Istituto Clinico Humanitas, Rozzano, Milano, Italy
[3]Abteilung für Neurologie, Oberschwabenklinik gGmbH, Ravensburg, Germany
[4]Department of Clinical and Experimental Sciences, Neurology Unit, University "Health and Wealth" of Brescia, Italy
[5]Stroke Unit, University of Debrecen, Hungary
[6]Department of Neurology, Keimyung University School of Medicine, Daegu, South Korea
[7]Stroke Unit-Department of Neurology, Santa Corona Hospital, Pietra Ligure (Savona), Italy
[8]Medical School and Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom.
[9]Centre Cérébrovasculaire, Service de Neurologie, Département des Neurosciences Cliniques Centre Hopitalier Universitaire Vaudois, Lausanne (Switzerland)

[10]Department of Neurology, Born Bunge Institute, Antwerp University Hospital, Antwerp, Belgium
[11]Stroke Unit, Neuroscience Department, University of Parma, Italy
[12]Stroke Unit - Dipartimento Geriatrico Riabilitativo – University of Parma, Italy
[13]Clinica Neurologica – Azienda Ospedaliero-Universitaria, Pisa, Italy
[14]SSO Stroke Unit, UO Neurologia, DAI di Neuroscienze, AOUI Verona, Italy
[15]Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland
[16]Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden
[17]Department of Internal Medicine, Cecina Hospital, Cecina, Livorno, Italy
[18]Stroke Unit, AOU Senese, Siena, Italy
[19]Department of Neurology, Democritus University of Thrace, University Hospital of Alexandroupolis, Greece
[20]International Clinic Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic
[21]Second Department of Neurology, "Attikon" Hospital, University of Athens, School of Medicine, Athens, Greece
[22]UO Gravi Cerebrolesioni, San Giovanni Battista Hospital, Foligno
[23]Stroke Unit, Department of Neurology, Sant'Andrea Hospital, La Spezia, Italy
[24]Department of Internal Medicine, Insubria University, Varese, Italy
[25]Stroke Unit, Neurology, Insubria University, Varese, Italy
[26]Stroke Unit, Ospedale di Portogruaro, Portogruaro (Venice), Italy
[27]Department of Neurology, University of L'Aquila, Italy
[28]Department of Internal Medicine, Ospedale Civile di Piacenza, Italy
[29]Municipal Budgetary Healthcare Institution of Novosibirsk. City Clinical Hospital #1. Novosibirsk (Russia)
[30]Stroke Unit, Jazzolino Hospital, Vibo Valentia, Italy
[31]Department of Neurology and Psychiatry, Sapienza University of Rome, Italy
[32]Stroke Unit, Ospedale Civico, Palermo
[33]Department of Neurology, Dresden University Stroke Center, Dresden, Germany
[34]Neurology, Hamad Medical Corporation, Doha, Qatar

Corresponding author:
Monica Acciarresi
Stroke Unit and Division of Internal and Cardiovascular Medicine
University of Perugia, Santa Maria della Misericordia Hospital
Via G. Dottori 1, Perugia
06100 – Italy
Email: macun77@hotmail.com
Tel and fax: ++39(0)75.5782765

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Abstract

Background and Purpose: The aim of this study was to investigate for a possible association between both pre-stroke CHA_2DS_2-VASc score and the severity of stroke at presentation as well as disability and mortality at 90 days in patients with acute stroke and atrial fibrillation (AF).

Methods: This prospective study enrolled consecutive patients with acute ischemic stroke, AF and assessment of pre-stroke CHA_2DS_2-VASc score. Severity of stroke was assessed at admission by the National Institute of Health Stroke Scale (NIHSS) score, (severe stroke: NIHSS≥10). Disability and mortality at 90 days were assessed by the modified Rankin Scale (mRS<3 or ≥3). Multiple logistic regression was used to correlate pre-stroke CHA_2DS_2-VASc and severity of stroke as well as disability and mortality at 90 days.

Results: Of the 1.020 patients included in the analysis, 606 patients had an admission NIHSS score lower and 414 patients higher than 10. At 90 days, 510 patients had mRS≥3. A linear correlation was found between pre-stroke CHA_2DS_2-VASc score and severity of stroke (p=0.001). On multivariate analysis, CHA_2DS_2-VASc score correlated with the severity of stroke (p=0.041) and adverse functional outcome (mRS≥3) (p=0.001). A logistic regression with the ROC graph procedure (C statistic) evidenced an area under the curve of 0.60 (p=0.0001) for severe stroke. Furthermore, a correlation was found between pre-stroke CHA2DS2-VASc score and the lesion size.

Conclusions: In patients with AF, in addition to the risk of stroke, a high CHA_2DS_2-VASc score was independently associated with both stroke severity at onset and disability and mortality at 90 days.

Background and Purpose

In patients with atrial fibrillation (AF), current guidelines recommend using the CHA_2DS_2-VASc score to assess the risk of stroke[1]. In retrospective studies CHA_2DS_2-VASc score have been suggested as a predictor of severity of stroke at admission and poor outcome[2–4].

The aim of this study was to investigate for a possible association between both pre-stroke CHA_2DS_2-VASc score and the severity of stroke at presentation as well as disability and mortality at 90 days in patients with acute stroke and atrial fibrillation (AF).

Methods

Data for this analysis were extracted from the database of a prospective multicentre study which had enrolled consecutive patients with acute stroke and AF (the RAF study)[5]. This study, carried out between January 2012 and March 2014, enrolled 1,029 consecutive patients from 29 Stroke Units throughout Europe and Asia.

Pre-stroke CHA_2DS_2-VASc score was evaluated as previously described[5]. On admission, the severity of acute stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS); all investigators were certified on the use of this scale. Disability and mortality at 90 days were assessed using the modified Rankin Scale (mRS).

Data on known stroke risk factors were collected as reported in the main paper[5].

A cerebral computed tomography (CT) or magnetic resonance (MR) was performed on admission for all patients to exclude intracranial hemorrhage. A second cerebral CT scan or MR was performed 48-72 h from stroke onset. The sites and sizes of the qualifying infarcts were determined based on standard templates [6,7] as previously described [5].

Statistical analysis

The primary pre-specified a priori study question was if CHA2DS2-VASc score had been associated with stroke severity assessed by NIHSS at onset. Then, as a post-hoc analysis,

possible correlations between CHA2DS2-VASc scores and outcome assessed by mRS and between CHA2DS2-VASc scores and lesion size were investigated for.

The admission NIHSS score was evaluated both as a continuous variable for the correlation coefficient r analysis, and dichotomized variables (severe stroke NIHSS≥10) for the multivariate analysis.

The correlation coefficient r, Pearson product-moment correlation coefficient, was used to measure the strength of the linear association between CHA_2DS_2-VASc before the event and NIHSS score on admission (as continuous variable).

Correlations between pre-stroke CHA_2DS_2-VASc and severity of stroke were sought by multiple logistic regression after adjusting for the following variables: smoking, hyperlipidemia, alcohol abuse and use of statins in addition to CHA_2DS_2-VASc.

Thereafter, the probability of a receiver-operating characteristic (ROC) curve against NIHSS≥10 as dependent variable was plotted. The area under this curve suggests an ability of the CHA2DS2-VASc score to predict for severe stroke, which is also referred to as the C-statistic (Harrell's C).

In addition, a multiple logistic regression model including components singularly of the CHA2DS2-VASc was performed.

Stroke was defined as either non-disabling (mRS 0 to 2) or disabling (mRS 3 to 5).

The factors evaluated as independent predictors of 3 month adverse outcome (defined as modified Rankin scale ≥3 or death) were assessed using multiple logistic regression analysis. The variables included in the model were CHA_2DS_2-VASc score, cardiovascular risk factors, reperfusion therapy and severity of stroke on admission according to NIHSS score.

The sites and sizes of the qualifying infarcts showed at CT scan were determined based on standard templates as follows: (1) small, when a lesion was ≤1.5 cm in the anterior or posterior circulation, (2) medium, when a lesion was in a cortical superficial branch of middle cerebral artery [MCA], in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery [PCA], in the PCA

branch or in a cortical superficial branch of the anterior cerebral artery [ACA]), (3) large anterior, when a lesion involved the complete territory of ACM, ACP, or ACA, in 2 cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in more than 1 artery territory [eg, MCA associated to ACA territories]), (4) large posterior, when a lesion was ≥1.5 cm in the brain stem or cerebellum[8].

A possible correlation between lesion size and CHA2DS2-VASc score was investigated for using a χ-squared (p for trend).

Results:

Overall, 1,029 consecutive patients were included in the study (mean age 77.2 ± 9.5 years; 560 females and 469 males). The distribution of CHA_2DS_2-VASc score in the study patients is reported in the Table 1.

Nine patients were excluded from the analysis as their NIHSS score was not available. Of the 1.020 patients included in the analysis, 606 patients had an admission NIHSS score lower and 414 patients higher than 10. The mean NIHSS score for each of the CHA_2DS_2-VASc scores are reported in the Table 1 (p=0.071). A linear correlation was found between severity of stroke and CHA_2DS_2-VASc score (r^2 0.010, p=0.001) (fig. 1). On multivariate analysis, CHA_2DS_2-VASc score correlated with the severity of stroke (OR 1.084, 95% CI 1.003-1.172, p=0.041, for each one point increase). Considering the modest correlation, a logistic regression with a ROC graph procedure, to get the c statistic, was performed and it evidenced that the area under the curve was 0.60 (0.56-0.63), p=0.0001 for severe stroke.

When factors included in the CHA2DS2-VASc score were assessed individually for a correlation between stroke severity, only increasing age and female sex resulted being significantly correlated to stroke severity according to NIHSS (p=0.007 and p =0.001, respectively) (Table 2).

A correlation was also found between pre-stroke CHA_2DS_2-VASc score and lesion size. After excluding patients treated with revascularization, 70% of patients with CHA_2DS_2-

VASc score of 8 or 9 had a medium-large lesion, while 70% of patients with CHA_2DS_2-VASc score of 0 had a small lesion (Figure 2, p for trend=0.042).

At 90-days, 1.019 patients were available for the functional outcome analysis (10 patients were lost at follow-up). The correlation between pre-stroke CHA_2DS_2-VASc score and 90 day outcome is reported in Table 1.

On multivariate analysis, both NIHSS score on admission and CHA_2DS_2-VASc score were correlated with disability and mortality at 90 days (mRS≥3) (OR 1.236, 95% CI 1.197-1.277, p<0.0001; OR 1.278; 95% CI 1.100-1.484, p=0.001 respectively for each ~~one~~ point increase).

The administration of thrombolytic therapy and the use of statins at admission resulted being independently correlated with better outcome (OR 0.313, 95% CI 0.204-0.481, p<0.0001; OR 0.585, 95% CI 0.354-0.967, p=0.036; respectively).

Discussion:

The results of our study found correlations between pre-stroke CHA_2DS_2-VASc score and severity of stroke at presentation, according to NIHSS, as well as between CHA2DS2-VASc score and 90-day mortality and disability, as measured by mRS.

Therein, indicating that a higher CHA2DS2-VASc score is predictive of a worse outcome.

Moreover, in post-hoc analyses we also found, first, a correlation between higher CHA2DS2-VASc score and greater lesion size. This finding could support previous studies that have reported an association between CHA2DS2-VASc score and major vessel occlusion in patients with acute ischemic stroke and AF [9]. Second, our study results also is in line with past studies reporting that among risk factors, age and female sex are more predictive of severe stroke[10,11].

A strength of this study was that several stroke assessment scores were prospectively utilized, and each of these scores were correlated to the CHA2DS2-VASc score. Whereas, several past studies were retrospective and used only a single assessment score[2–4,12–14].

In conclusion, we found an increasing CHA2DS2-VASc score in AF patients predicted a more severe stroke at presentation, leading to a higher rate of disability and mortality at 90 days. This result highlights the need for physicians to more regularly investigate for AF in patients with other known vascular risk factors, especially increasing age and female sex.

Table 1: Stroke severity (NIHSS) and 90 day outcome according to pre-stroke CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	**Pre-stroke CHA_2DS_2-VASc (n=1029)**	**NIHSS at admission (mean)^ (n=1020**)**	**90-day mRS score≥3* (n=1019***)**
0	17 (1.7%)	5.18 ± 5.75	4/17 (23.5%)
1	54 (5.2%)	8.30 ± 8.16	16/53 (30.2%)
2	91 (8.9%)	8.31 ± 6.70	34/90 (37.7%)
3	200 (19.4%)	8.86 ± 7.10	81/198 (40.9%)
4	243 (23.6%)	9.12 ± 7.22	125/242 (51.6%)
5	206 (20.0%)	9.67 ± 7.73	113/202 (55.9%)
6	129 (12.8%)	9.70 ± 6.50	78/129 (60.5%)
7	66 (6.4%)	10.30 ± 8.20	43/65 (66.1%)
8-9	23 (2.2%)	12.09 ± 6.68	16/23 (69.6%)

^p for trend=0.071

*p for trend=0.0001

** Nine patients were excluded from the analysis as their NIHSS score was not available

***1019 patients were available for the final functional outcome analysis (10 patients were lost at follow-up)

Table 2. Multivariate analysis for correlation of stroke severity and any of each component of CHA2DS2-VASC score.

	OR	**P**	**95% CI**
Age (for each year increase)	1.020	0.007	1.005-1035
Sex	0.367	0.001	0.515-0.175
Diabetes	1.172	0.296	0.870-1.575
Hypertension	0.759	0.110	0.542-1.065
Stroke/TIA/Thromboembolism	0.972	0.849	0.723-1.306

History			
Congestive Heart Failure	1.049	0.777	0.753-1.462
Vascular Disease	1.034	0.832	0.760-1.406

Fig. 1. Linear correlation between NIHSS at admission and CHA2DS2-VASC score.

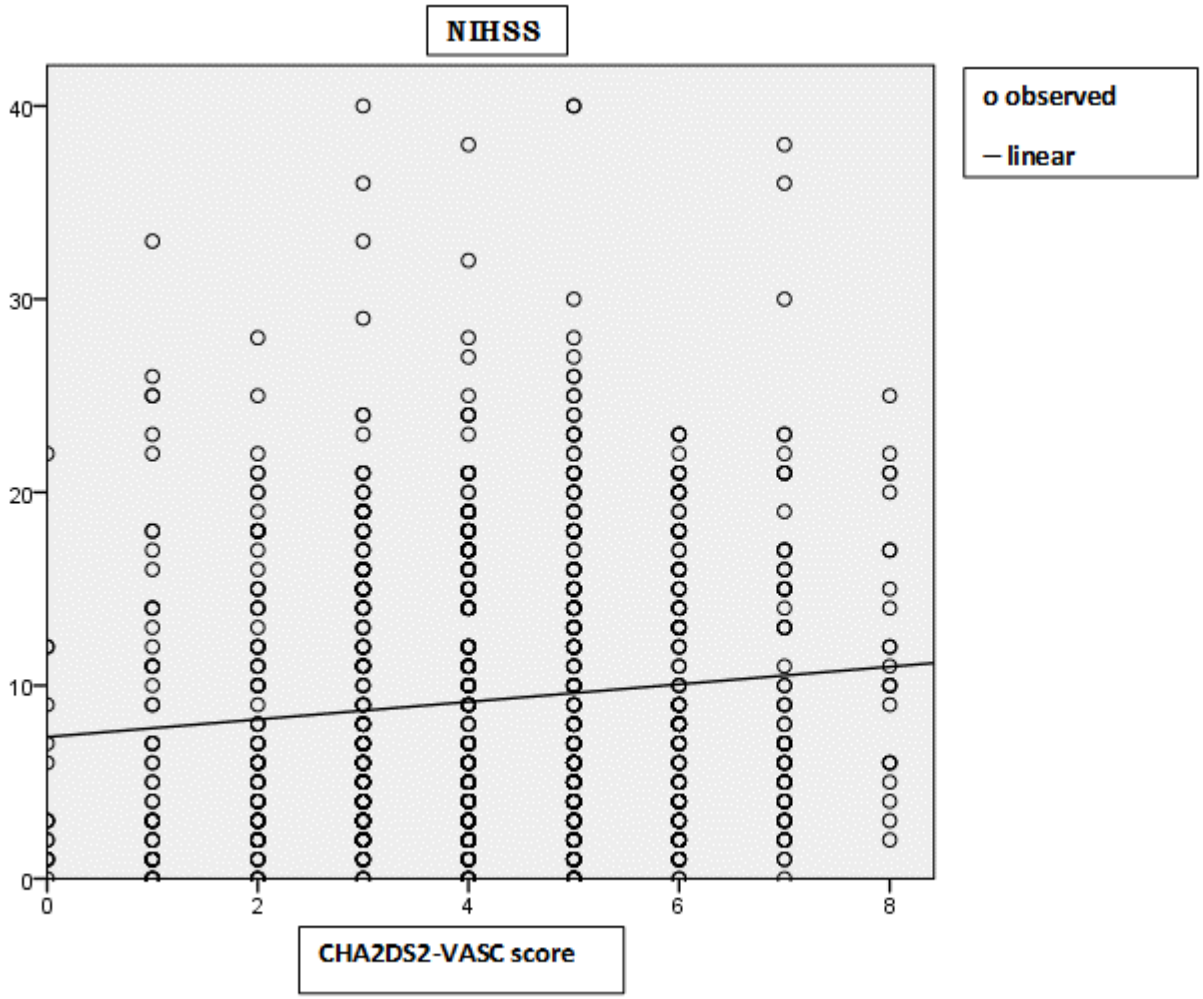
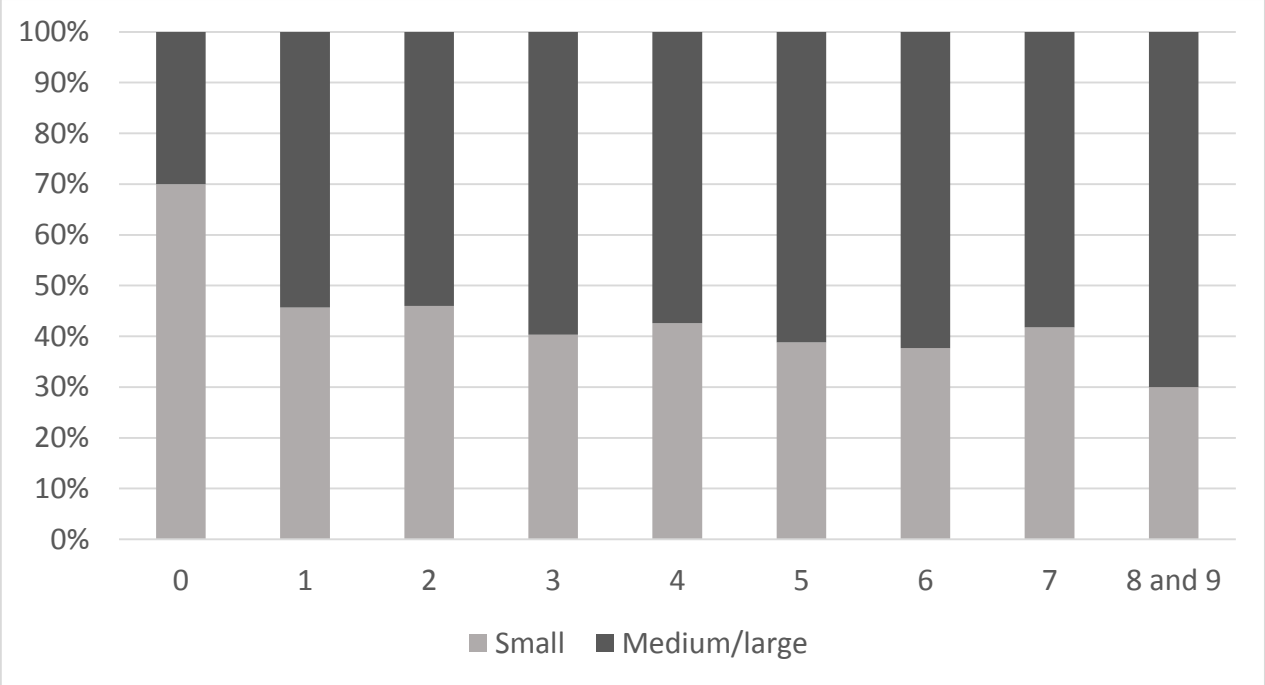


Figure 2: CHA_2DS_2-VASC score and lesion size (excluding patients treated with revascularization).



* p for trend=0.042

Disclosures

On behalf of all authors, the corresponding author states that there is no conflict of interest.

M. Paciaroni received honoraria as a member of the speaker bureau of Sanofi-Aventis, Boehringer Ingelheim, Bayer and Pfizer. G. Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer. C. Becattini received honoraria as a member of the speaker bureau of Bristol Meyer Squibb and Bayer. P. Michel received Research Grant by Swiss National Science Foundation and Swiss Heart Foundation; he received speaker fees by Bayer, Boehringer Ingelheim, Covidien, St. Jude Medical; he received honoraria as advisory relationship by Pierre-Fabre, Bayer, Bristol Meyer Squibb, Amgen, and Boehringer Ingelheim. J. Putaala received honoraria for lectures related to atrial fibrillation and anticoagulants for Orion Pharma, Bristol Meyer Squibb, Pfizer,

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